recommended by the manufacturer. Dissociated and dithiothreitol-reduced immunocomplexes were separated by SDS-polyacrylamide gel electrophoresis (SDS-PAGE) and electroblotted onto nitrocellulose using a Trans-Blot Semi-Dry Transfer Cell (Bio-Rad, Laboratories, Inc., Hercules, CA). After overnight incubation of membranes in PBS containing 10% dry nonfat milk, 0.05% TWEEN 20 and 0.02% Na-azide, they were repeatedly washed in TST [0.15 M NaCl, 10 mM Tris-OH (pH 7.4), 0.3% TWEEN 20] and reacted with avidin-horseradish peroxidase (Vector Laboratories Inc., Burlingame, CA) in TST (2.5 μg/ml) for 1 hour at 4° C. Membranes washed with TST were treated with ECL enhanced chemiluminescent reagent (Amersham, Life Science, Arlington Heights, IL) and exposed to X-ray film. For pulse-labeling and chase, 5 x 10^6 cells per time point were labeled with 0.5 mCi [^{35}S]methionine for 5 min. as described (Grandea *et al.,* 1995). For chase, cells were spun through PBS with 10 mM methionine and resuspended in growth media for the indicated time periods. Cells were lysed, and MICA protein was precipitated using mAB 2C10 as described above. Isolated and denatured MICA was treated with endoglycosidase H (Endo H, New England Biolabs) as recommended by the manufacturer and analysed by SDS-PAGE. Fixed gels were treated with AMPLIFY (Amersham) and dried for autoradiography.

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REMARKS

I. Status of the Claims/Formalities

Claims 1-101 were filed with the original application. Claims 26-101 stand withdrawn pursuant to a restriction requirement, and are canceled herein. Claims 1-25 are presently pending in the application and stand rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. The specific grounds for rejection and applicants' response to them are set forth in detail below.

An amendment updating the priority information at page 1 of the application is provided.

II. Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1-25 are pending in the application and stand rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention. The examiner argues that several statements in the specification are unclear. Specifically, the examiner mentions the word "involvement," in the statement, "an involvement of MICA with colon carcinoma" on page 10, line 1-4, and the phrase, "variable amounts," in the statement "variable amounts of MICA were detected on endothelial tumor cell lines such as HT29 colon carcinoma and U373 astrocytoma cells ...." on page 76, lines 24-26. The examiner also argues that "it is not clear that the expression of MICA in two endothelial cell lines is indicative of the expression of MICA or MICB in actual endothelial cancers ...." Finally, the examiner argues that the specification does not "exemplify detecting a cancer cell in said sample comprising identifying expression of MICA or MICB in said sample" because the state of the art does not teach the expression of MICA or MICB in cancer cells. Applicants respectfully traverse.

In order for a patent to satisfy the enablement requirement, it "must contain a description that enables one skilled in the art to make and use the claimed invention ...." *DeGeorge v. Bernier*, 768 F.2d 1318, 1323, 226 U.S.P.Q. 758, 762 (Fed. Cir. 1985), citing *In re Howarth*, 654 F.2d 103, 105, 210 U.S.P.Q. 689, 691 (C.C.P.A. 1981). Furthermore, "[a]n inventor need not, however, explain every detail since he is speaking to those skilled in the art." *Id.* The inventor must provide "sufficient information about the claimed invention that a person of skill in the field of the invention can make use of the invention without undue experimentation ...." *Scripps Clinic v. Genentech*, 927 F.2d 1565, 1571, 18 U.S.P.Q.2d 1001, 1006 (Fed. Cir. 1991). However, "[n]othing more than objective enablement is required, and therefore it is irrelevant

whether this teaching is provided through broad terminology or illustrative examples." *In re Wright*, 999 F.2d 1557, 1561-62, 27 U.S.P.Q.2d 1510 (Fed. Cir. 1993). "That some experimentation may be required is not fatal; the issue is whether the amount of experimentation is 'undue.'" *In re Vaeck*, 947 F.2d 488, 495, 20 U.S.P.Q.2d 1438, 1444 (Fed. Cir. 1991).

In essence, the examiner is not arguing that the specification contains insufficient ***instruction*** to those of skill in the art, but rather, that the specification does not convince the examiner (or one of skill in the art) that the claimed invention is operable. Put another way, the examiner simply disbelieves that one can identify tumor cells based up the expression of MICA and/or MICB. Applicants now will address and refute the examiner's specific "reasons" for this concern.

First, applicants respectfully disagree that use of the term "involvement" creates, in any way, and question of clarity. Page 7, lines 5-6 of the specification state that "[t]he present inventors have determined that MICA and MICB are ***expressed at the cell surface*** of colon and other cancer cells." Emphasis added. Thus, applicants use of the term "involvement" is clear.

Second, applicants also disagree that the phrase "variable amounts" raises any problems. As discussed on page 75, lines 6-9, "indirect immunofluorescence studies showed that ***large*** amounts of MICA were present on ... HT29 colon carcinoma and U373 astrocytoma cell lines." Emphasis added. Thus, one of ordinary skill in the art would reasonably have understood that MICA was overexpressed on tumor cells, thereby providing the basis for the claimed invention.

Third, the examiner argues that "it is not clear that the expression of MICA in two endothelial cell lines is indicative of the expression of MICA or MICB in actual endothelial cancers ...." As an aside, applicants respectfully point out that the examiner has mistakenly discussed "endothelial" cancer cell lines rather than "epithelial" cancer cell lines. Regardless,

the examiner's offering of "it is not clear" does not provide the basis for an enablement rejection (see *Marzocchi*, above). Moreover, the cell lines in question (HT29 and U373) are derived from actual malignant colon adenocarcinoma and astrocytoma tumors. Astrocytoma tumors occur most commonly in the brain and occasionally in the spinal cord. Adenocarcinoma tumors can occur in the colon, lung, esophagus, prostate, stomach, or in any organ with glandular epithelial tissue. This list of cancers easily encompasses most of the cancers recited in claims 24 and 25.

Fourth, the examiner contends that the art, at the time of filing, teaches that MICA and MICB are "almost exclusively made in the gastrointestinal epithelium, as evidenced by Groh *et al.* (1996), but does not indicate expression as being associated with cancer cells." That may very well be, but that simply defines the present invention as ***novel and nonobvious***, and it most certainly does not undercut enablement, *i.e.*, prove that MICA and MICB are not tumor antigens.

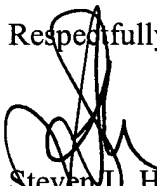
Fifth, the examiner continues by arguing that "it would require undue experimentation for one of skill to predict which if any types of cancer cells could be detected ...." Once again, applicants disagree. The presence of MICA and MICB in astrocytoma and colon carcinoma cell lines, as supported by page 75, lines 6-9 and page 76, lines 24-25, which clearly show that MICA and MICB are associated with a wide variety of cancers (see above). Furthermore, articles published subsequent to the filing date support the present claims. Takehara *et al.* (2003) show expression of MICA and MICB in hepatocellular carcinoma, and Groh *et al.* (1999) report that freshly isolated tumor specimens from carcinomas of the lung, breast, kidney, ovary, prostate and colon express MICA and MICB. Thus, just as the present application alleges, and the present claims recite, MICA and MICA can be used to identify many different tumors, and only routine experimentation is required to employ this invention.

Therefore, applicants respectfully submit that the examiner has not advanced a *prima facie* case of non-enablement, and if advanced, applicants have provided sufficient rebuttal evidence to establish that MICA and MICB can, in fact, be used as the basis for cancer identification. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

III. Conclusion

Applicants submit that, in light of the foregoing, all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should the examiner have and questions regarding this response, a telephone call to the undersigned is invited.

Respectfully submitted,



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